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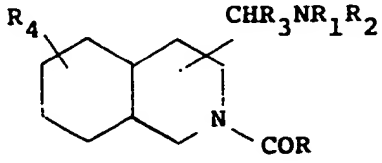
(54) Title: DECAHYDROISOQUINOLINE COMPOUNDS



(I)

(57) Abstract

A compound, or a solvate or salt thereof of formula (I), in which RCO is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring; R_1 and R_2 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups, or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, optionally substituted with a hetero-atom, provided that R_1 and R_2 are not simultaneously hydrogen; R_3 is hydrogen, C_{1-6} alkyl, or phenyl, or R_3 together with R_1 form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group; and R_4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or halogen.

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Decahydroisoquinoline compounds.

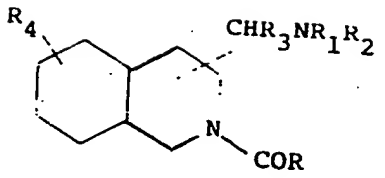
This invention is concerned with novel decahydro-isoquinoline derivatives, processes for their preparation, and their use in medicine, particularly as analgesics.

Compounds which are kappa-receptor agonists act as analgesics through interaction with kappa opioid receptors. The advantage of kappa-receptor agonists over the classical μ-receptor agonists, such as morphine, lies in their ability to cause analgesia while being devoid of morphine-like behavioural effects and addiction liability.

European Published Application No. 232989 (Beecham Group p.l.c.) discloses a group of isoquinoline derivatives which exhibit kappa-receptor agonism without some of the behavioural effects of morphine and morphine analogues, and which are thus of potential therapeutic utility as analgesics and/or as anti-hyponatraemic agents and/or as anti-cerebral ischaemia agents.

A novel class of structurally related heterocyclic derivatives has now been discovered which also exhibit potent kappa-receptor agonism without the aforementioned undesirable behavioural effects.

According to the present invention there is provided a compound, or a solvate or salt thereof, of formula (I):



(I)

in which:

RCO is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring;

R_1 and R_2 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups, or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, optionally substituted with a hetero-atom,
provided that R_1 and R_2 are not simultaneously hydrogen;

R_3 is hydrogen , C_{1-6} alkyl, preferably methyl or ethyl, or phenyl, or R_3 together with R_1 form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

and R_4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or halogen, preferably methyl, methoxy or chlorine.

When used herein, the term 'carbocyclic aromatic group' includes single or fused rings, having 6 to 12 ring carbon atoms, and the term 'heterocyclic aromatic group' includes single or fused rings having 5 to 12 ring atoms, comprising up to four hetero-atoms in the or each ring, selected from oxygen, nitrogen and

sulphur.

When the carbocyclic or heterocyclic group is a fused two ring system, one or both rings may be aromatic in character.

Suitably, one of the rings is aromatic and the other is non-aromatic.

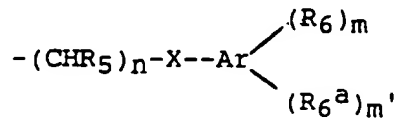
The C_{1-6} alkyl groups may be either straight or branched chain and examples are methyl, ethyl, propyl, n-butyl, n-pentyl or n-hexyl, preferably methyl.

Examples of C_{2-6} alkenyl groups are 1- and 2-propenyl; an example of a C_{3-6} cycloalkyl group is cyclopropyl, and an example of a C_{4-12} cycloalkylalkyl group is cyclopropyl methyl.

When R_1 and R_2 together form a linear or branched polymethylene group, examples are propylene, butylene, pentylene or hexylene, preferably butylene or 1-methyl-butylene. As an alkylene group, R_1-R_2 may be typically $-CH_2-CH=CH-CH_2-$. Examples of hetero-atoms are oxygen and sulphur, particularly oxygen, and a suitable hetero-atom substituted polymethylene group is $-CH_2CH_2OCH_2CH_2-$.

When R_1 and R_2 are both C_{1-6} alkyl, they are preferably methyl.

The group R preferably has the formula (II):



(II)

in which n is 0, 1 or 2;

m is 0, 1 or 2;

m' is 0, 1 or 2, provided $m + m' \leq 2$;

X is a direct bond, or O, S or NR_7 in which R_7 is hydrogen or C_{1-6} alkyl;

Ar is a substituted or unsubstituted carbocyclic or heterocyclic group,

R_5 is hydrogen or C_{1-6} alkyl, such as methyl or ethyl;

each of R_6 and R_6^a is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, aralkyl, hydroxy, C_{1-6} alkoxy, thiol, C_{1-6} alkylthio, C_{1-6} haloalkoxy, C_{1-6} haloalkylthio, halogen, NO_2, CN, CF_3, $-OCF_3$, $-OCHF_2$, $-OCF_2CF_2H$, $-OCCl_2CF_3$, $-COOR_8$, $-CONR_9R_{10}$, $-SO_3R_{11}$, $-SO_2NR_{12}R_{13}$ and $-COR_{14}$ in which each of R_8 to R_{14} is independently hydrogen, C_{1-6} alkyl, aryl or aralkyl;

or, when m is 2 and m' is 0, two R_6's form a C_{2-6} polymethylene group,

Preferred halogens are F, Cl and Br.

When two R_6's are linked they preferably form a fused cyclopentyl or cyclohexyl ring.

Preferably Ar is phenyl and R_6 or R_6^a is preferably in the meta and/or para position.

Preferably R_6 or R_6^a is bromine, chlorine, NO_2 or CF_3, particularly in the meta- or para- position.

More preferably R_6 or R_6^a is chlorine.

X is typically oxygen or a direct bond, and n is typically 0 or 1.

The $-CHR_3NR_1R_2$ group is preferably located at the 1 or 3 position on the heterocyclic ring system, and R_4 is preferably located at the 5 position.

The compounds of formula I or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula I or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Examples of a pharmaceutically acceptable salt of a compound of formula I include the acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Examples of a pharmaceutically acceptable solvate of a compound of formula I include the hydrate.

The compounds of formula I have more than one asymmetric centre and therefore exist in more than one stereoisomeric form. The invention extends to all such forms and to mixtures thereof, including racemates.

Examples of compounds of the invention are:

1-(N,N-dimethylamino)methyl-2-(3,4-dichlorophenyl)-acetyl-decahydroisoquinoline maleate;

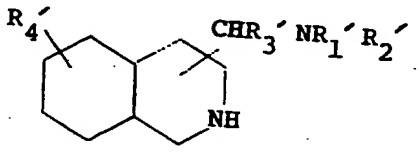
1-(N,N-dimethylamino)methyl-2-(3,4-dichlorophenyl)acety l-decahydroisoquinoline hydrochloride;

1-(pyrrolidin-1-yl)methyl-2-(3,4-dichlorophenyl)acetyl-decahydroisoquinoline maleate;

2-(3,4-dichlorophenyl)acetyl-3-(N,N-dimethylamino)-methyl-decahydroisoquinoline hydrochloride;

2-(3,4-dichlorophenyl)acetyl-3-(pyrrolidin-1-yl)methyl-decahydroisoquinoline.

The present invention also provides a process for the preparation of a compound of formula I which comprises reacting a compound of formula (III):



(III)

in which R_1', R_2', R_3' and R_4' are R_1, R_2, R_3 and R_4 as defined for formula I, or are groups or atoms convertible to R_1, R_2, R_3 and R_4,

with a compound of formula R'CO.OH or an activ derivative thereof,

in which R' is R as defined for formula (I), or a group or atom convertible to R, to form a compound of formula I(a):

(Ia)

and then optionally performing one or more of the following steps:

a) where R', R_1', R_2', R_3' or R_4' are other than R, R_1, R_2, R_3 or R_4 respectively, converting R', R_1', R_2', R_3' or R_4' to R, R_1, R_2, R_3 or R_4 respectively, to obtain a compound of formula (I),

b) where R', R_1', R_2', R_3' or R_4' are R, R_1, R_2, R_3 or R_4 respectively, converting one R, R_1, R_2, R_3 or R_4 respectively to another R, R_1, R_2, R_3 or R_4 respectively to obtain a compound of formula (I),

c) forming a salt and/or solvate of the obtained compound of formula (I).

Suitable active derivatives of R'-C(=O)-OH are acid chlorides or acid anhydrides. Another suitable derivative is a mixed anhydride formed between the acid and an alkyl chloroformate.

For example, in standard methods well known to those

skilled in the art, the compound of formula (III) may be coupled:

a) with an acid chloride in the presence of an inorganic or organic base,

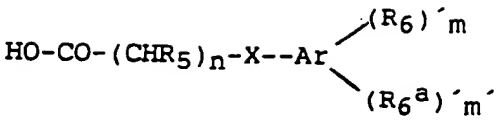
b) with the acid in the presence of dicyclohexyl carbodiimide, N-dimethylaminopropyl-N'-ethyl carbodiimide or carbonyl diimidazole,

c) with a mixed anhydride generated in situ from the acid and an alkyl (for example ethyl)chloroformate.

It will be appreciated that a compound of formula (Ia) may be converted to a compound of formula (I), or one compound of formula (I) may be converted to another compound of formula (I), by interconversion of suitable substituents. Thus certain compounds of formula (I) and (Ia) are useful intermediates in forming other compounds of the present invention.

R_1' and R_2' may be alkyl groups and converted to R_1'/R_2' hydrogen atoms by conventional amine dealkylation. When R_1' or R_2' is benzyl or substituted benzyl it may be converted to an R_1 or R_2 hydrogen atom by catalytic hydrogenation or other conventional methods of reduction. R_1' and R_2' as hydrogen atoms may be converted to R_1 and R_2 alkyl groups by conventional amine alkylation, or by acylation followed by reduction. R_1' and R_2' are preferably R_1 and R_2 respectively.

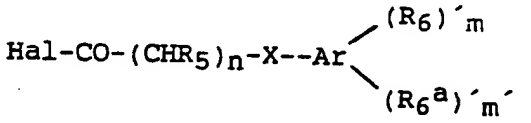
The compound $R'-\overset{O}{\overset{\|}{C}}-OH$ is typically of the formula (IIa)



(IIa)

in which R_6' is R_6 and $(R_6^a)'$ is R_6^a are as defined for formula (II), or a group or atom convertible to R_6 or R_6^a respectively, the other variables being as defined for formula (II).

A preferred compound is the equivalent acid halide of formula (IIb)



(IIb)

in which Hal is halogen, typically chlorine or bromine.

Conversions of substituents R_6' or $(R_6^a)'$ on the aromatic group Ar to obtain R_6 or R_6^a are generally known in the art of aromatic chemistry.
R_6' is preferably R_6 and $(R_6^a)'$ is preferably R_6^a.

The compounds of formula (I) may be converted into their pharmaceutically acceptable acid addition salts by reaction with the appropriate organic or mineral acids.

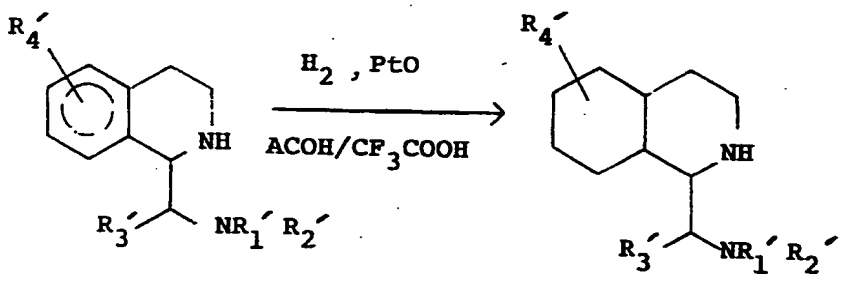
Solvates of the compounds of formula I may be formed by crystallization or recrystallization from the appropriate solvent. For example hydrates may be formed by crystallization or recrystallization from aqueous solutions, or solutions in organic solvents containing water.

Also salts or solvates of the compounds of formula I

which ar not pharmaceutically acceptable may be useful as intermediates in the production of pharmaceutically acceptable salts or solvates. Accordingly such salts or solvates also form part of this invention.

The compounds of formula I exist in more than one stereoisomeric form and the processes of the invention produce mixtures thereof. The individual isomers may be separated one from another by standard physico-chemical methods (eg column chromatography or fractional crystallisation). The single enantiomers may be separated by resolution using an optically active acid such as tartaric acid. Alternatively, an asymmetric synthesis would offer a route to the individual form.

The compounds of formula (III) bearing the $CHR_3'NR_1'R_2'$ substituent in position 1 (i.e. compounds of formula IIIa) may be obtained by catalytic hydrogenation of a compound of formula (IV), for example by hydrogenation in a mixture of acetic and trifluoroacetic acid in the presence of a platinum oxide catalyst.

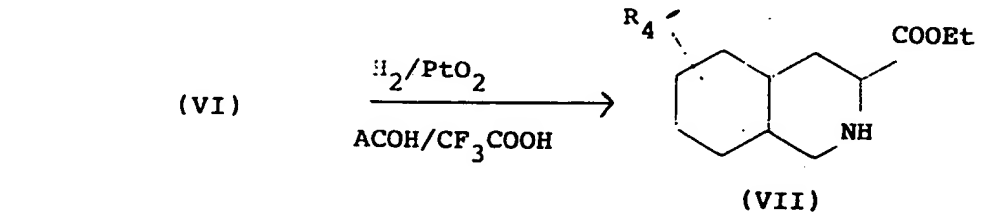


(IV) (IIIa)

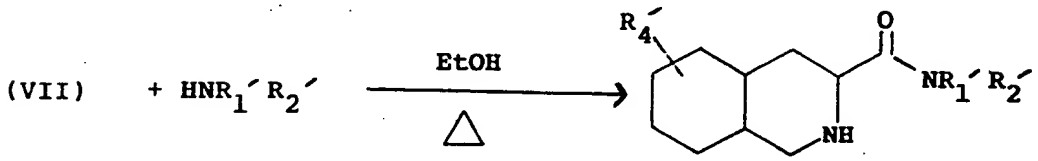
Compounds of formula (IV) are known compounds or can be obtained from known compounds by known methods (see for example European Published Application No. 232989)

(Beecham Group p.l.c.)).

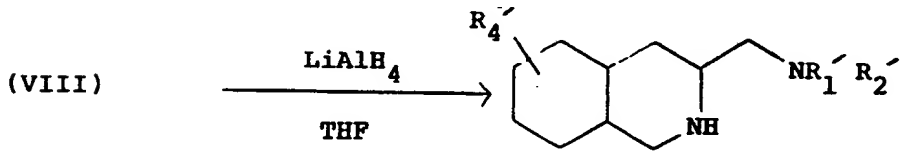
The compounds of formula (III) bearing the $CHR_3'NR_1'R_2'$ substituent in position 3 (i.e. compounds of formula IIIb) may be obtained from a compound of formula (VIII) by reduction with a mixed hydride, such as $LiAlH_4$, in a solvent such as THF at room temperature, in accordance with the following reaction scheme:



(VII)



(VIII)



(IIIb)

As outlined in th above reaction scheme, the compounds of formula (VIII) may themselves be prepared by reacting a compound of formula (VII) with an amine of formula $HNR_1'R_2'$ in a solvent, such as EtOH, at an elevated temperture, such as 90°C. The compounds of formula (VII) may themselves be prepared from compounds of formula (VI) by catalytic hydrogenation in a solvent mixture such as ACOH/CF_3COOH, with a catalyst such as platinum oxide.

The compounds formula (VI) may themselves be prepared from compounds of formula (V) by known methods, such as for example by warming a compound of formula (V) in the presence of $SOCl_2$ in a solvent such as EtOH.

The compounds of formula (V) are known compounds or may be prepared from known compounds by known methods (see for example Hayashi et al (Chem. Pharm. Bull. 31, 312, 1983) and European Published Application No. 228246).

Certain intermediates described above are novel compounds and, together with the described processes for their preparation, they form a further aspect of this invention.

The activity of the compounds of formula (I) as kappa agonists indicates that they are of therapeutic utility in the treatment of pain and/or hyponatraemic disease states and/or of cerebral ischaemia.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of pain and/or hyponatraemic disease states and/or cerebral ischaemia.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known analgesic agents and/or anti-hyponatraemic agents and/or anti-cerebral ischaemia agents.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of pain and/or of hyponatraemic disease states and/or of cerebral ischaemia.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and

on the condition of the patient. It will also dep nd, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tableting or the like.

Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan mono-oleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be

administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

As mentioned earlier, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

Within the above indicated dosage range, no adverse toxicological effects have been observed with compounds of the invention.

The present invention also provides a method of treating pain and/or hyponatraemic disease states and/or cerebral ischaemia in mammals, particularly in humans, which comprises administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, to a sufferer.

Compounds of this invention and their preparation are illustrated in the following Examples.

Description 1

1-(N,N-dimethylamino)methyl-decahydroisoquinoline

9.5 g (50 mmoles) of 1-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydroisoquinoline (mixture of diastereoisomeric diamines) was dissolved in a mixture of 40 ml CH_3COOH and 10 ml of CF_3COOH and 0.4 g of PtO_2 added. The mixture was hydrogenated in a Parr hydrogenation apparatus at a pressure of 40 psi and a temperature of 50°C until the theoretical amount of hydrogen had been absorbed.
The catalyst was filtered off and the reaction mixture evaporated in vacuo to dryness, taken up with a 40% NaOH solution and extracted with Et_2O. The organic layer was washed with a NaCl saturated solution and evaporated in vacuo to afford 9.18 g (93.5% yield) of the title compound, as an oil, which was used in example 1 without further purification.

Alternatively,
1-(pyrrolidin-1-yl)methyl-1,2,3,4-decahydroisoquinoline was obtained, as an oil, in an analogous manner, and used in example 3 without further purification.

Example 1

1-(N,N-dimethylamino)methyl-2-(3,4-dichlorophenyl)acetyl-decahydroisoquinoline diastereoisomer A maleate

4.3 g (22 mmoles) of 1-(N,N-dimethylamino)methyl-decahydroisoquinoline of Description 1 were dissolved in 80 ml of dry chloroform and the solution cooled to -5°C.
5.3 g (23.7 mmoles) of 3,4-dichlorophenylacetyl chloride, dissolved in 27 ml of dry chloroform, were added dropwise and the solution allowed to reach room temperature and left overnight.
The reaction mixture was washed with 30 ml of 32% of NH_4OH solution, and the organic layer separated, dried over Na_2SO_4 and evaporated in vacuo to dryness. The crude product obtained was chromatographed on silica gel eluting with CH_2Cl_2 containing increasing amounts of MeOH (0.1-2.5%) to

afford the 1 ast polar product which was crystallized as its maleat to yield 1.5 g of the title compound.

$C_{24}H_{32}Cl_2N_2O_5$

M.P. = 195°C
M.W. = 499.426

Elemental analysis: Calcd. C, 57.11; H, 6.46; N, 5.61
Found C, 57.77; H, 6.50; N, 5.63

Example 2

1-(N,N-dimethylamino)methyl-2-(3,4-dichlorophenyl)acetyl-decahydroisoquinoline diastereoisomer C hydrochloride

Continuing the elution of the chromatographic column of the Ex. No. 1, after a small amount of a second product which was not isolated, a third product was obtained and crystallized as its hydrochloride to yield 0.25 g of the title compound.

$C_{20}H_{29}Cl_3N_2O$

M.P. = 205°C
M.W. = 419.819

Elemental analysis: Calcd. C,57.21; H,6.95; N,6.67; Cl,25.34
Found C,57.36; H,7.17; N,6.44; Cl,24.56

Example 3

1-(pyrrolidin-1-yl)methyl-2-(3,4-dichlorophenyl)acetyl-decahydroisoquinoline diastereoisomer A maleate

Prepared as Ex. No. 1, from 6.8 g (30.5 mmoles) of 1-(pyrrolidin-1-yl)-1,2,3,4-decahydroisoquinoline (obtained as in Description 1) and 6.9 g (30.9 mmoles) of 3,4-dichlorophenylacetylchloride in dry chloroform. The work up of the reaction mixture was carried out as described in Ex. No. 1.

The distereoisomer A was obtained as its maleate from acetone and crystallized from EtOH to yield 0.75 g of the title compound.

$C_{26}H_{34}Cl_2N_2O_5$

M.P. = 183°C
M.W. = 525.462

Elemental analysis: Calcd. C,59.42; H,6.52; N,5.33; Cl,13.49
Found C,59.38; H,6.55; N,5.34; Cl,13.41

Description 2

3-carboxyethyl-decahydroisoquinoline

20 g (97.4 mmoles) of 3-carboxyethyl-1,2,3,4-tetrahydroisoquinoline (obtained by reaction of 3-carboxy-1,2,3,4-tetrahydroisoquinoline and thionyl chloride in ethanol), dissolved in a mixture of 150 ml of AcOH and 20 ml of CF_3COOH, and 0.7 g of platinum oxide were hydrogenated in a Parr hydrogenator at a pressure of 40 Psi and a temperature of 40°C until complete absorption of the theoretical amount of hydrogen. The catalyst was filtered off, the reaction mixture was evaporated in vacuo to dryness, taken up with a 40% NaOH solution and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and evaporated in vacuo to dryness, to afford 7.2 g (35% yield) of the title compound as an oil, which was used in Description 3 without further purification.

Description 3

3-(N,N-dimethylamino)carbonyl-decahydroisoquinoline

3.6 g (17 mmoles) of 3-carboxyethyl-decahydroisoquinoline (from Description 2) were added to 25 ml of a 33% ethanolic solution of dimethylamine (183 mmoles) and maintained at 90°C for fifteen days. The reaction mixture was then evaporated in vacuo to dryness to yield 3.7 g of an oil which was used for the subsequent reaction without further purification.

Alternatively,
in an analogous manner,4 g of 3-(pyrrolidin-1-yl)carbonyl-decahydroisoquinoline was obtained as a crude oil from 3.4 g (16.1 mmoles) of 3-carboxyethyl-decahydroisoquinoline and 12 g (168.7 mmoles) of pyrrolidine in 10 ml of EtOH.

Description 4

3-(N,N-dimethylamino)methyl-decahydroisoquinoline

A solution of 1 g of $LiAlH_4$ in 10 ml of THF was added dropwise under stirring at 25°C to a solution of 3.7 g of the crude 3-(N,N-dimethylamino)carbonyl-decahydroisoquinoline of Description 3, and left overnight.
The reaction mixture was taken up with a mixture of THF and 40% NaOH solution and filtered on randalite. The mother liquors were evaporated in vacuo to dryness, taken up with a conc. NaOH solution and extracted with Et_2O to afford 3.3 g of the title compound,as an oil,which was used for the subsequent reaction without further purification.

3.6 g of 3-(pyrrolidin-1-yl)methyl-decahydroisoquinoline were obtained by an analogous procedure starting from 4 g of 3-(pyrrolidin-1-yl)carbonyl-decahydroisoquinoline.

Example 4

2-(3,4-dichlorophenyl)acetyl-3-(N,N-dimethylamino)methyl-decahydroisoquinoline diastereoisomer A hydrochloride

3.3 g (16.8 mmoles) of 3-(N,N-dimethylamino)methyl-decahydroisoquinoline of Description 4 were dissolved in 20 ml of dry chloroform and cooled to -5°C.
4.1 g (18.3 mmoles)of 3,4-dichlorophenylacetyl chloride in 20 ml of dry chloroform were added dropwise and the solution allowed to reach room temperature and left overnight.
The reaction mixture was washed with 15 ml of 32% NH_4OH solution and the organic layer separated, dried over Na_2SO_4 and concentrated in vacuo to dryness. The crude product obtained was chromatographed on silica gel eluting with CH_2Cl_2 containing increasing amounts of methanol (0.1-2.5%) to afford the least polar product which was crystallized as its hydrochloride to yield 2 g of the title compound.

$C_{20}H_{29}Cl_3N_2O$

M.P. = 186-8°C
M.W. = 419.819

Elemental analysis: Calcd. C,57.71; H,6.96; N,6.67; Cl,25.34
Found C,54.80; H,6.76; N,6.63; Cl,26.91

Example 5

2-(3,4-dichlorophenyl)acetyl-3-(pyrrolidin-1-yl)methyl-decahydroisoquinoline diastereoisomer A

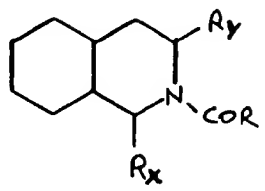
Prepared as Ex. No. 4 from g 3.6 (16.2 mmoles) of 3-(pyrrolidin-1-yl)methyl-decahydroisoquinoline (obtained as in Description 4) and 4.1 g (18.3 mmoles) of 3,4-dichlorophenylacetyl chloride in dry chloroform.
The work up of the reaction mixture was carried out as described in Ex. No. 1.
The title compound was obtained as the free base as a oil.

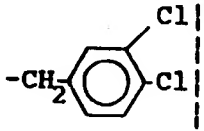
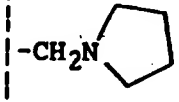
$C_{22}H_{30}Cl_2N_2O$

M.W.= 409.39

For the compounds of Ex. from 1 to 5 the NMR and IR data are in agreement with the proposed structures.

Table 1



Example No	R	Rx	Ry	Molecular Formula	M.W.	M.P. (°C)
1 (Diast. A)		$-CH_2NMe_2$	H	$C_{20}H_{28}Cl_2N_2O \cdot C_4H_4O_4$	499.426	195
2 (Diast. C)	"	"	"	$C_{20}H_{28}Cl_2N_2O.HCl$	419.819	205
3 (Diast. A)	"		"	$C_{22}H_{30}Cl_2N_2O \cdot C_4H_4O_4$	525.462	183
4 (Diast. A)	"	H	$-CH_2NMe_2$	$C_{20}H_{28}Cl_2N_2O.HCl$	419.819	186-188
5 (Diast. A)	"	"		$C_{22}H_{30}Cl_2N_2O$	409.39	Oil

The pharmacological activity of the compounds of this invention is illustrated by various in vitro and in vivo models, using the following test procedures, in which the mouse tail flick test demonstrates analgesic activity.

The results of the tests are given in Table 2

Tail-flick test in mice

The methodology employed is based on that described by D'Amour and Smith, J. Pharmacol. Exp. Ther. 72, 74/1941.

Male Charles River mice (Swiss Strain), 22-34 g body weight are used. Animals are allowed food and water ad libitum and are randomized into groups of 10 prior to experimentation. Before administration of the test compound, the reaction time of each animal is determined by focusing a beam of light onto the tail, eliciting a reflex withdrawal after a certain latency; only mice exibiting a latency between 3-8 sec. are used subsequently in the evaluation of drug effects.

Test compounds are dissolved in either distilled water or distilled water plus 0.1 M AMS and administered by the subcutanous route in a final volume of 10 ml/Kg. Control animals receive 10 ml/kg of the appropriate vehicle alone. Following a pretreatment period of 30 min., the mice are again placed under the heat source and the reaction time re-determined.
Percentage quantal protection is determined as the number of mice in which the reaction time is doubled compared to pretreatment values, expressed as a percentage of the total number of mice in the group.

RECEPTOR AFFINITY STUDY -GUINEA PIG BRAIN

Tissue Preparation

Radio receptor binding to μ, k and δ sites is performed on fresh guinea pig brain homogenate prepared according to Kosterlitz. (1981).
Whole brain without cerebellum, is homogenized in 50 mM Tris-buffer (pH 7.4 at 0°C) and centrifuged again.
The pellet is then resuspended in the same buffer, incubated at 37°C for 45 min. and centrifuged again.
1.9 ml of the final homogenate (1:100 in Tris-pH 7.4, 0°C) is used f r the binding assay.

Binding to k sites (Magnan J., 1982)

The binding to the k-sites is performed using ^{3}H-EthylKetocyclazocine, a non-selective benzomorphan compound which binds to μ, δ and k sites, in the presence of 100 nM of unlabelled DAGO and 100 nM of the enkephalin analogue [DAla^2-DLeu^5] Enkephalin (DADLE), to prevent μ and δ binding respectively.
Final homogenate with solutions of the cold ligand and of the labelled ligand is incubated for 40 min. at 25°C, filtered through Whatman GF/C glass filter discs and washed. The radioactivity bound to the filters is counted by liquid scintillation spectrophotometry.
The non-specific binding is determined in the presence of 500 nM of the benzomorphan non-selective compound, Mr 2266.

References:

- Hill, A.V. (1910): J Physiol. 40, IV-VIII (1910)
- Scatchard G. (1949): Ann. N.Y. Acad.Sci., 51, 660-674
- Cheng and Prusoff W.H. (1973): Biochem Pharmac. 22, 3099-3102

- Kosterlitz H.W., Paterson S.Y. and Robson L.E. (1981) : Br. J. Pharmac. 73, 939-949
- Magnan J., Paterson S.Y., Tavani A. and Kosterlitz H.W. (1982) : Arch. Pharmacol. 319, 197-205

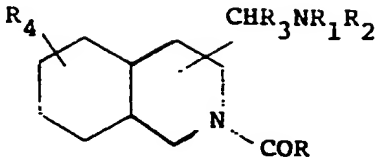
Table 2

PHARMACOLOGICAL DATA

Example No	IN VIVO TEST MOUSE TAIL-FLICK		RECEPTOR AFFINITY STUDY BINDING TO K SITES
	DOSE (mg/kg)	% ANALGESIA	Ki Kappa (nM)
1	9.1	100	> 100
2	9.1	40	> 100
3	9.2	100	1-100
4	9.1	60	> 100
5	1.34	50	10-50

CLAIMS :

1. A compound, or a solvate or salt thereof, of formula (I):



(I)

in which:

RCO is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring;

R_1 and R_2 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups, or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, optionally substituted with a hetero-atom,
provided that R_1 and R_2 are not simultaneously hydrogen;

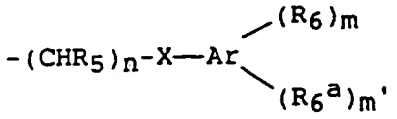
R_3 is hydrogen , C_{1-6} alkyl, or phenyl, or R_3 together with R_1 form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

and R_4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or halogen.

2. A compound according to claim 1, in which each of R_1 and R_2 is methyl, ethyl, propyl, butyl, pentyl or hexyl.

3. A compound according to claim 1, in which each of R_1 and R_2 together form a propylene, butylene, pentylene or hexylene group, or a $-CH_2-CH=CH-CH_2-$ group.

4. A compound according to anyone of claims 1 to 3, in which R has the formula (II):



in which n is 0, 1 or 2;
m is 0, 1 or 2;
m' is 0, 1 or 2, provided $m + m' \leq 2$;
X is a direct bond, or O, S or NR_7 in which R_7 is hydrogen or C_{1-6} alkyl;
Ar is a substituted or unsubstituted carbocyclic or heterocyclic group,

R_5 is hydrogen or C_{1-6} alkyl, such as methyl or ethyl;

each of R_6 and R_6^a is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, aralkyl, hydroxy, C_{1-6} alkoxy, thiol, C_{1-6} alkylthio, C_{1-6} haloalkoxy, C_{1-6} haloalkylthio, halogen, NO_2, CN, CF_3, $-OCF_3$, $-OCHF_2$, $-OCF_2CF_2H$, $-OCCl_2CF_3$, $-COOR_8$, $-CONR_9R_{10}$, $-SO_3R_{11}$, $-SO_2NR_{12}R_{13}$ and $-COR_{14}$ in which each of R_8 to R_{14} is independently hydrogen, C_{1-6} alkyl, aryl or aralkyl;
or, when m is 2 and m' is 0, two R_6's form a C_{2-6} polymethylene group,

5. A compound according to claim 4 wherein Ar is phenyl and R_6 or $R_6{}^a$ is chlorine.

6. A compound selected from:

1-(N,N-dimethylamino)methyl-2-(3,4-dichlorophenyl)-acetyl-decahydroisoquinoline maleate;

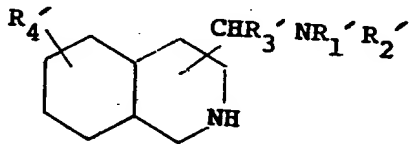
1-(N,N-dimethylamino)methyl-2-(3,4-dichlorophenyl)-acetyl-decahydroisoquinoline hydrochloride;

1-(pyrrolidin-1-yl)methyl-2-(3,4-dichlorophenyl)acetyl-decahydroisoquinoline maleate;

2-(3,4-dichlorophenyl)acetyl-3-(N,N-dimethylamino)-methyl-decahydroisoquinoline hydrochloride; and

2-(3,4-dichlorophenyl)acetyl-3-(pyrrolidin-1-yl)methyl-decahydroisoquinoline.

7. A process for the preparation of a compound of formula I as defined in claim 1 which comprises reacting a compound of formula (III):



(III)

in which R_1', R_2', R_3' and R_4' are R_1, R_2, R_3 and R_4 as defined in claim 1 for formula I, or are groups or atoms convertible to R_1, R_2, R_3 and R_4, with a compound of formula R'CO.OH or an active

derivative thereof,

in which R´ is R as defined for formula (I), or a group or atom convertible to R, to form a compound of formula I(a):

(Ia)

and then optionally performing one or more of the following steps:

a) where R´, R_1´, R_2´, R_3´ or R_4´ are other than R, R_1, R_2, R_3 or R_4 respectively, converting R´, R_1´, R_2´, R_3´ or R_4´ to R, R_1, R_2, R_3 or R_4 respectively, to obtain a compound of formula (I),

b) where R´, R_1´, R_2´, R_3´ or R_4´ are R, R_1, R_2, R_3 or R_4 respectively, converting one R, R_1, R_2, R_3 or R_4 respectively, to another R, R_1, R_2, R_3 or R_4 respectively, to obtain a compound of formula (I),

c) forming a salt and/or solvate of the obtained compound of formula (I).

8. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

9. A method of treating pain and/or hyponatraemic disease states and/or cerebral ischaemia in mammals, particularly in humans, which comprises administering an effective amount of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or solvate thereof, to a sufferer.

10. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof for use as an active therapeutic substance.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 89/01621

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 217/14, A 61 K 31/47

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC5	C 07 D; A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A2, 0232989 (DR. LO. ZAMBELETTI S.P.A.) 19 August 1987, see claims 1, 8, 10	1-8, 10
P,A	EP, A2, 0330469 (GLAXO GROUP LIMITED) 30 August 1989, see the abstract	1-6,8, 10
P,A	EP, A1, 0330360 (DR. LO. ZAMBELETTI S.P.A.) 30 August 1989, see the abstract; claims 1, 9	1-8, 10

* Special categories of cited documents: [14]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
5th April 1990	24. 04. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MISS D. S. KOWALCZYK

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FR M THE SE OND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Derwent's abstract no. 08576X/05, SU 622-400 see the abstract --	1-6,8, 10

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 9, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv):
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/EP 89/01621

SA 33554

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/02/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0232989	19/08/87	AU-D-	6791587	30/07/87
		JP-A-	62240665	21/10/87
		US-A-	4806547	21/02/89
EP-A2- 0330469	30/08/89	AU-D-	3029389	24/08/89
EP-A1- 0330360	30/08/89	AU-D-	3007089	24/08/89